$R_{6'}$ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3; and

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl.

REMARKS

I. Claim Amendments

Independent claims 1, 7, 18 and 19 have been amended to emphasize the special technical feature that defines the contribution which each of the claimed inventions makes over the prior art. Specifically, the special technical feature is an extended blood plasma profile of an H^+, K^+-ATPase inhibitor which is induced by the claimed administration regimen (claims 1-6, 18 and 20), oral pharmaceutical formulation (claims 7-11, 19 and 21) and method of treatment (claims 15, 16 and 22). As such, the scope of the claimed invention is not limited to just the H^+, K^+-ATPase of the general formula I, but rather encompasses any compound defined as an H+, K+-ATPase inhibitor. Accordingly, claims 1, 7, 18 and 19 have been amended to broadly define the active ingredient as an H^+, K^+-ATPase inhibitor. The recitation of the H^+, K^+-ATPase of the general

formula I has been deleted from the same claims, and is now embodied in new dependent claims 20 and 21.

Support for the invention as broadly claimed by the amended claims is found on page 1, lines 5-16, of the specification as originally filed. Applicants submit, therefore, that no new matter has been added by any of the amendments.

II. Election/Restriction

A restriction requirement under 35 U.S.C. §§121 and 372 was issued. Specifically, it is alleged that the subject application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept as required by PCT Rule 13.1:

Group I: claims 1-11, 15, 16, 18 and 19, drawn to an administration regimen, pharmaceutical formulation and method of treatment, wherein Het_1 is a substituted pyridine and Het_2 is a benzimidazole classified in Class 546 and 514 and Subclasses 273.4 and 339;

Group II: claims 1-11, 15, 16, 18 and 19, drawn to an administration regimen, pharmaceutical formulation and method of treatment, wherein Het_1 is a substituted pyridine and Het_2 is an imidazo thiophene classified in Class 548 and 514 and Subclasses 303.7 and 339;

Group III: claims 1-11, 15, 16, 18 and 19, drawn to an administration regimen, pharmaceutical formulation and method of treatment, wherein Het_1 is a substituted carbocyclic ring and Het_2 is a benzimidazole classified in various subclasses in Class 568 and 514; and

Group IV: claims 1-11, 15, 16, 18 and 19, drawn to an administration regimen, pharmaceutical formulation and method of treatment, wherein Het_1 is a substituted carbocyclic ring and Het_2 is an imidazo thiophene classified in various subclasses in Class 568, 548 and 514.

During a telephone conversation with the Examiner on April 21, 1999, the undersigned attorney provisionally elected, with traverse, the invention of Group I for examination purposes. That provisional election, with traverse, is hereby affirmed.

III. Traversal of the Restriction Requirement

The subject application is the national stage application of international application PCT/SE97/01098. The claims of the subject national stage application, as originally filed, are substantially similar if not identical to the claims of the international application. Although only claims 7-14 of the international application were examined, there was no holding of lack of unity by the International Preliminary Examining Authority. In other words, claims 7-14 were examined by the International Authorities without a requirement that Applicants elect a species of the compound of the formula I for examination purposes. In this regard, the Examiner's attention is directed to the International Preliminary Examination report which was received by the U.S.P.T.O. on 21 October 1997.

It appears incongruous, therefore, that the Examiner has reached a different conclusion regarding unity of invention in view of the same PCT Rules 13.1 and 13.2 as embodied in 37 C.R. §1.475(a). Accordingly, Applicants respectfully submit that the Examiner is unfairly and unjustly applying a more rigorous standard in evaluating unity of invention in the national stage application than that standard which was applied in the related international application.

Furthermore, examination of the subject application may not contravene the relevant rules of either the PCT or the U.S. patent laws. Specifically, according to PCT Rule 13.2 and 37 C.F.R. §1.475(a), the overriding criterion regarding unity of invention among a group of inventions is the existence of "a technical relationship among those inventions involving one or

more of the same or corresponding special technical features". The expression ***special technical feature*** means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

In the subject national stage application, as well as in the related international application, the special technical feature of each of the claimed inventions is an extended blood plasma profile of an H^+, K^+-ATPase inhibitor which is induced by the claimed administration regimen (claims 1-6, 18 and 20), oral pharmaceutical formulation (claims 7-11, 19 and 21) and method of treatment (claims 15, 16 and 22). Patentability is based on Applicants' unexpected discovery that a repeated regimen or a dosage form which provides an extended plasma profile of an H+, K+-ATPase inhibitor produces a measurable improvement in the inhibition of gastric acid secretion. The extended blood plasma profile of the H+, K+-ATPase inhibitor is the special technical feature linking the inventions of Groups I-IV as well as defining the inventions of Groups I-IV over the prior art.

Therefore, it is Applicants position that the claims, as originally filed, satisfy the statutory requirement of unity of invention. There is a technical relationship among each of the claimed inventions involving the same technical feature, i.e., an extended blood plasma profile of an H+, K+-ATPase inhibitor. In order to give emphasis to this special technical feature, claims 1, 7, 18 and 19 have been amended to broadly define the active ingredient as an H^+, K^+-ATPase inhibitor. The recitation of the H^+, K^+-ATPase of the general formula I, which forms the basis for the Restriction Requirement, has been deleted from the independent claims and is now embodied in new dependent claims 20 and 21.

Finally, there is precedent that the instant claims, as amended, relate to a single inventive concept under PCT Rules 13.1 and 13.2. In this regard, the Examiner's attention is directed to U.S. Patent No. 5,753,265 to Bergstrand et al. (the "'265 patent") which was cited as prior art relative to the claimed invention. Claim 1 of the '265 patent is directed to an oral pharmaceutical composition in the form of a multiple unit tablet comprising an H^+, K^+-ATPase inhibitor as the active ingredient. Claim 2 of the '265 patent defines the H^+, K^+-ATPase inhibitor of claim 1 as being a compound of the same general formula I of the present application. The substituents Het_1 are identical for the general formula I of the '265 patent and the present application. The substituents Het_2, as defined at col. 20, lines 16-25 of the '265 patent, are identical to the substituents Het_2 of the present application. Moreover, the combinations of Het_1 and Het_2 in claim 2 of the '265 patent present many more possible compounds in comparison to the compounds of claims 20 and 21 of the subject application. Nevertheless, the Patent Office determined that the H^+, K^+-ATPase inhibitor, as the active ingredient, provided a technical relationship among the inventions of the claims of the '265 patent. Accordingly, for the same reason, the claims of the present application relate to one invention and, as such, there is unity of invention.

In summary, therefore, the restriction requirement is improper and should be withdrawn for the following reasons:

- There was no holding of lack of unity of invention by the International Preliminary Examining Authority upon examination of the claims in the related international application.
- The extended blood plasma profile of the H^+, K^+-ATPase inhibitor is the ***special technical feature*** linking the inventions of Groups I-IV as well as defining the inventions of Groups I-IV over the prior art; therefore, the requirements of PCT Rules 13.1 and 13.2 are satisfied.
- As evidenced by claims 1 and 2 of the cited '265 patent, the Patent Office has determined that the inventions of the claimed invention are linked as to form a single general inventive concept under PCT Rule 13.1

IV. The Claimed Invention

The claimed invention is directed to the advantageous and unexpected discovery that a repeated regimen or a dosage form which provides an extended plasma profile of an H^+, K^+-ATPase inhibitor produces an improvement in the inhibition of gastric acid secretion.

In order to appreciate the novel and non-obvious aspects of the claimed invention, one must first understand that the pharmacological effect of a proton pump inhibitor, such as omeprazole, is not dependent on the plasma concentration of the drug itself. For example, whereas the duration of acid inhibition of omeprazole is 3-4 days, the plasma half-life of the same drug is only 0.5-1 hour. Despite the long duration of acid inhibition, a single daily dosage of

omeprazole results in 75-80% inhibition of maximal acid output prior to the next dose. Therefore, about 20 to 25% of the maximal gastric acid secretory capacity is present 24 hours after a daily dose of the drug. The administered proton pump inhibitor reacts with the active gastric acid pumps available for inhibition during that time. However, due to the short plasma half-life of the proton pump inhibitor, the plasma concentration of the drug is ineffective to block the inactive pumps of parietal cells as they become active.

Accordingly, there was a need for an improvement in treating gastric acid secretion. The claimed invention provides a solution in the form of an administration regimen or dosage form by which an extended plasma profile of the proton pump inhibitor is obtained. The extended plasma profile ensures that the plasma concentration of the drug will be sufficient to block previously inactive gastric acid pumps.

The Examiner's attention is directed to the Example and Figure of the subject application. As described in the Example at pages 10 and 11, the pharmacological effect of the claimed administration regimen was compared with a conventional administration regimen involving omeprazole. Pursuant to the invention, a first group of subjects received 20 mg of omeprazole twice daily with 3 hours apart from each administration. A second group of subjects received a single 40 mg daily dose of omeprazole. With each group of subjects, the efficacy of the respective administration regimen in controlling acid secretion was measured. As shown in the Figure, the therapeutic effect of omeprazole is maximized, particularly on "day 1", when the blood plasma concentration of the drug is extended by repeated single doses of omeprazole which are administered with 3 hours apart from each administration.

Applicants submit that the substantial improvement in efficacy as shown in Figure 1 is evidence of a patentable discovery. ***In view of the prolonged degree and duration of acid***

inhibition, e.g., 3-4 days, it was indeed unexpected that a repeated regimen or a dosage form which provides an extended blood plasma concentration of an H^+, K^+-ATP-ase inhibitor, as claimed, would have an improved pharmacological effect in the inhibition of gastric acid secretion.

V. Claim Rejections - 35 U.S.C. §112

The phrase "characterized by" has been removed from the amended claims. As suggested by the Examiner, the phrase "inhibitor having the formula I" has been replaced with the recommended phrase "inhibitor of formula I".

VI. Claim Rejections - 35 U.S.C. §102

Claims 1-11, 15, 16, 18 and 19 are rejected under 35 U.S.C. §102(e) as being anticipated by the '265 patent and U.S. Patent No. 5,817,338 to Bergstrand et al. (the "'338 patent"). The '265 and '338 patents are directed to multiple tablet formulations comprising a proton pump inhibitor as the core material. The gist of the '265 and '338 patents is the core material in the form of enteric coated pellets, wherein the enteric coating layer has properties which minimize the reduction of acid resistance of the coated pellets which are compressed during tableting.

Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. For anticipation, there must be no difference between the claimed invention and the reference, as viewed by a person of ordinary skill in the field of the invention. Applicants submit that neither the '265 nor the '338 patent discloses each and every element of the claimed invention.

Claims 1-6, 18 and 20 are directed to an administration regimen which induces an extended blood plasma profile of an H^+, K^+-ATPase inhibitor. Although the '265 and '338 patents disclose an administration regimen of daily doses one to several times a day (the '265 patent at col. 10, lines 36-42; the '338 patent at col. 8, lines 59-61), there is no disclosure of the claimed special technical feature, i.e., a repeated regimen or dosage form which provides an extended blood plasma profile of an H^+, K^+-ATPase inhibitor to maximize the effectiveness of the drug. Applicants submit that the administration regime of the '265 and '338 patents, as broadly disclosed by the cited art, is consistent with the typical administration regimen of pharmaceuticals, i.e., increase the dosage or frequency to increase the pharmacological effect of the drug. Typically, a single daily dose of omeprazole is prescribed and administered. In instances where a single daily dose is inadequate to provide relief, the doctor may prescribed repeated single dosages every 12 hours.

However, it warrants repeating at this time to emphasize that the pharmacological effect of a proton pump inhibitor, such as omeprazole, is not dependent on the plasma concentration of the drug itself. The prolonged degree and duration of acid suppression would dictate against the need for consecutive administrations of omeprazole. Therefore, it is indeed contrary to the prior art that the pharmacological effect of a proton pump inhibitor could be significantly improved, as demonstrated by the Example and Figure of the subject application, by a repeat regimen of an H^+,K^+-ATPase inhibitor. As disclosed in the specification at page 5, lines 6-15, the administration regimen of the claimed invention also encompasses an extended and constant release of the H^+,K^+-ATPase inhibitor which follows the pharmacokinetics of the repeat administration of the Example. Applicants submit that neither the '265 nor the '338 patent discloses these aspects of the claimed invention as particularly embodied by claims 1 and 2.

Additionally, claim 3 recites a specific administration regimen of ***a dosage interval of 0.5-4 hours*** which is not disclosed by the cited references. The administration regimen of claim 4 is based on the ***absorption of the proton pump inhibitor in two or more discrete pulses separated in time by 0.5-4 hours***. This feature of claim 4 is not disclosed by the cited references. As recited by claim 5, the proton pump inhibitor is released for ***absorption with an almost constant rate during an extended time period and the extended plasma profile is maintained for 2-12 hours***. The recited features of claim 5 are not disclosed by the cited references. Claim 6 recites ***an extended plasma profile of 2-12 hours*** which is not disclosed by the cited references. Accordingly, the cited references fail to disclose each and every element of the claimed administration regimen as described by claims 1-6, 18 and 20.

Claims 7-11, 19 and 21 are directed to an oral pharmaceutical formulation which induces an extended blood plasma profile of an H+, K+-ATPase inhibitor. As previously discussed, the '265 and '338 patents disclose a typical administration regimen of daily doses one to several times a day. As such, there is no disclosure of a pharmaceutical formulation wherein the drug is repeatedly administered by ***an extended release***. The PCT family member (WO 96/01623) of the cited '338 patent was cited against the formulation claims of the international application from which the subject national stage application derives. The Examiner's attention is directed to the International Preliminary Examination Report where it is stated that the formulation claims are both novel and non-obviousness in view of WO 96/01623. The dosage forms of the '265 and '338 patents are administered one to several times a day. Thus, the drug is not administered by an extended release. Accordingly, the cited references fail to disclose each and every element of the claimed pharmaceutical formulation as described by claims 7-11, 19 and 21.

Claims 15, 16 and 22 are directed to methods of treatment comprising the administration of the pharmaceutical formulation of claims 7-11. Applicants submit that claims 15, 16 and 22 are novel for the same reasons that the composition claims 7-11, 19 and 21 are novel in view of the cited '265 and '338 patents.

For all of the foregoing reasons, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 102(e).

VI. Claim Rejections - 35 U.S.C. §103

Claims 1-11, 15, 16, 18 and 19 are rejected under 35 U.S.C. §103(a) as being unpatentable over the '265 and '338 patents. As stated on page 6 of the Office Action, it is the Examiner's position that "[i]t would have been obvious...that extended release of the active ingredient would effect the blood concentration profile". Based on the Examiner's own statement, it is apparent that the Examiner has failed to appreciate the technological surprise underlying Applicants' discovery.

In order to avoid duplication, the Examiner is requested to revert to the preceding discussion under Section IV entitled "The Claimed Invention". ***In view of the prolonged degree and duration of acid inhibition, e.g., 3-4 days, it was indeed unexpected that a repeated regimen or a dosage form which provides an extended blood plasma concentration of an H^+, K^+-ATP-ase inhibitor, as claimed, would have an improved pharmacological effect in the inhibition of gastric acid secretion.*** This advantage and unexpected result is not suggested by the cited '265 and '338 patents. As noted by the Examiner in the international application from which the subject national stage application derives, WO 96/01623 discloses the general state of the prior art and, therefore, does not suggest the advantage which is possible with the claimed

invention. The prolonged pharmacological effect of an H^+, K^+-ATP-ase inhibitor would not have suggested the need or advantage of a repeated regimen or dosage form which provides an extended blood plasma concentration of the proton pump inhibitor. Applicants rely on the Example and Figure which substantiate the unexpected advantage of the claimed invention.

For all of the foregoing reasons, withdrawal of the rejection under 35 U.S.C. §103(a) in view of the '265 and '338 patents is requested.

Claims 1-11, 15, 16, 18 and 19 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,330,982 to Tyers (the "' 982patent"). The '982 patent discloses a combination therapy comprising a 5-HT receptor antagonist and an H^+, K^+-ATPase inhibitor. The two active ingredients may be administered as a single pharmaceutical composition (col. 2, lines 60-63). Alternatively, the two active ingredients may be co-administered in the form of two separate pharmaceutical compositions for simultaneous or sequential use (col. 2, lines 63-66). Preparations for oral administration may be formulated to give controlled release of one or both active ingredients (col. 10, lines 53-56).

The gist of the '982 patent is a combination therapy. The only example of the '982 patent is directed to a single dosage form, in the form of a tablet or syrup, comprising both active ingredients. The example is not directed to a controlled release formulation. Accordingly, without the benefit of hindsight, the '982 patent does not suggest the claimed invention comprising the administration of an H^+, K^+-ATP-ase inhibitor to induce an extended blood plasma blood profile of the H^+, K^+-ATP-ase inhibitor.

For all of the foregoing reasons, withdrawal of the rejection under 35 U.S.C. §103(a) in view of the '982 patent is requested.

CONCLUSION

The Amendment and Remarks set forth herein are fully responsive to the Office Action. It is respectfully submitted that claims 1-11, 15, 16 and 18-22 are in condition for allowance, which action is earnestly solicited.

Any additional fees in connection with this response should be charged to Deposit Account No. 23-1703.

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Respectfully submitted,

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